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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/536,502

12/14/2005

Chris D. Geddes

014835-101.02-029

6557

24239 7590 11/24/2009
MOORE & VAN ALLEN PLLC
P.O. BOX 13706
Research Triangle Park, NC 27709

EXAMINER

BERTAGNA, ANGELA MARIE

ART UNIT

PAPER NUMBER

1637

MAIL DATE

DELIVERY MODE

11/24/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<p align="center">Advisory Action Before the Filing of an Appeal Brief</p>	Application No. 10/536,502	Applicant(s) GEDDES ET AL.	
	Examiner Angela M. Bertagna	Art Unit 1637	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 November 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
 (b) ☐ They raise the issue of new matter (see NOTE below);
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
 5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
 6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
 The status of the claim(s) is (or will be) as follows:
 Claim(s) allowed: _____.
 Claim(s) objected to: _____.
 Claim(s) rejected: 1,5-10,12-16,18,20-22 and 24-27.
 Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
 12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
 13. ☐ Other: _____.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

Continuation of 5. Applicant's reply has overcome the following rejection(s): (i) the objection to the specification and (ii) the objections to claims 1, 4, 6, 8, 9, and 15.

Continuation of 7. Upon entry of the proposed amendment, claims 1, 5-10, 12-16, 18, 20-22, and 24-27 would be rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart in view of Gryczynski and further in view of Cao and further in view of Qi for the reasons made of record in the final rejection mailed on August 26, 2009. The proposed amendment incorporates the limitations of presently canceled claims 4 and 19 into claims 1 and 16, respectively. Since claims 4 and 19 were previously rejected under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Lockhart, Lakowicz (Gryczynski in the Office Action), Cao, and Qi, upon entry of the proposed amendment, claims 1, 5-10, 12-16, 18, 20-22, and 24-27 would remain rejected for the same reasons set forth in the final rejection.

Upon entry of the proposed amendment, claims 1, 5-10, 12-16, 18, 20-22, and 24-27 would be rejected under 35 U.S.C. 103(a) as being unpatentable over Cao as evidenced by Malicka and Lukomska in view of Lakowicz I and further in view of Lakowicz II for the reasons made of record in the final rejection mailed on August 26, 2009. The proposed amendment incorporates the limitations of presently canceled claims 4 and 19 into claims 1 and 16, respectively. Since claims 4 and 19 were previously rejected under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of the above references, upon entry of the proposed amendment, claims 1, 5-10, 12-16, 18, 20-22, and 24-27 would remain rejected for the same reasons set forth in the final rejection.

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments filed on November 5, 2009 have been fully considered, but they were not persuasive. As noted above, upon entry of the proposed amendment, claims 1, 5-10, 12-16, 18, 20-22, and 24-27 would be rejected for the same reasons set forth in the final rejection with regard to claims 1, 4-10, 12-16, 18-22, and 24-27. Accordingly, Applicant's arguments filed on November 5, 2009 remain pertinent to the rejections that would be made upon entry of the proposed amendment.

Regarding the rejection of claims 1, 4-10, 12-16, 18-22, and 24-27 as being unpatentable in view of the combined teachings of Lockhart, Lakowicz, Cao, and Qi, Applicant first argues that the combined teachings of the cited references do not teach or suggest the claimed invention. In particular, Applicant argues that Lockhart in Figures 12-13 only describes an array having a large number of arbitrarily selected probes and does not teach or contemplate the requirement for specific probes as required by the claimed methods (see pages 9-10).

This argument was not persuasive, because as discussed previously, Lockhart expressly teaches oligonucleotide capture probes that are immobilized on a solid support and complementary to a known sequence of a target nucleic acid (see, for example, page 9, line 21 - page 10, line 2, page 12, lines 3-15, page 20, lines 1-13, page 45, lines 7-30, and page 53, lines 21-30). Although Lockhart teaches at page 71 that different embodiments of the disclosed methods include the use of oligonucleotide probes that can be randomly selected, haphazardly selected, composition biased, inclusive of all possible oligonucleotides of a particular length, etc, the disclosed methods are not limited to these embodiments. Further regarding Applicant's arguments at pages 9-10, it is noted that the prior art is relevant for all that it contains or would have suggested to the ordinary artisan (MPEP 2123). In contrast to Applicant's arguments at page 9, the position of the Office did not change in the final rejection. Rather, the additional teachings cited were cited to rebut Applicant's specific arguments regarding the teachings of the Lockhart reference and demonstrate that the disclosure of the reference is more expansive than Applicant argues.

Applicant also argues that the labeled probes used in the method of Lockhart must include a ligatable oligonucleotide and a ligase (page 10). Applicant argues that this feature of the methods of Lockhart requires the free oligonucleotide probe to hybridize to the second portion of the target sequence at a position close enough to permit ligation and that the fluorescent label is located at the 5' end of the ligatable oligonucleotide probe (page 11). Applicant further argues that Lockhart does not recognize or discuss the importance of label placement in terms of its interaction with metallic particles on the substrate (page 11).

These arguments were not persuasive, because the importance of the label position relative to metallic particles on the substrate is discussed in the Lakowicz reference. As discussed above, an ordinary artisan would have been motivated by the teachings of Lakowicz to sandwich the fluorescent label used in the detection methods of Lockhart between metal particles in order to enhance the observed signal. It is further noted that the claimed methods recite open, "comprising" language, and therefore, do not exclude methods, such as the methods resulting from the combined teachings of the cited references, in which the free probe is ligated to the capture probe. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is further noted that Lockhart expressly teaches that the position of the fluorescent label is not limited to the 5' terminus so long as the labeled probe can undergo a ligation reaction (see, for example, page 10, lines 3-13 and also pages 40 and 42). It is also noted that, contrary to Applicant's arguments at page 11, the free probes used in the methods of Lockhart are not limited to embodiments where all possible lengths of free probes are used. The methods of Lockhart also encompass the use of free probes of the same length.

Applicant also argues that the secondary reference (Lakowicz) does not teach or suggest placement of the fluorophore on the free probe as required by the rejected claims (see pages 11-12). In particular, Applicant argues that the teachings of Lakowicz are directed to increasing the intrinsic fluorescence of nucleic acids rather than increasing the fluorescence of external fluorophores (pages 11-12). Applicant also argues that the only discussion in the reference pertaining to external fluorophores contains negative teachings that would lead the ordinary artisan away from sandwiching an external fluorophore, such as those disclosed by Lockhart (pages 11-12).

These arguments were not persuasive, because the teachings of Lakowicz cited by Applicant as negative teachings only discuss complications in one specific embodiment involving the use of fluorescently labeled nucleotides, specifically exonuclease-based

sequencing. As discussed previously, Lakowicz teaches that a limiting factor in exonuclease-based sequencing is the need to label each nucleotide after exonuclease catalyzed release from the target nucleic acid (see page 12 of the response, where the teachings of Lakowicz are reproduced). These teachings of Lakowicz do not appear to consider detecting external fluorescent labels to be problematic, but rather attaching external fluorescent labels to sequentially released nucleotides to be problematic. Since the methods of Lockhart are not directed to exonuclease-based sequencing and do not require the complicated post-cleavage labeling step required by exonuclease-based sequencing methods, the teachings of Lakowicz would not have lead the ordinary artisan away from using metallic particles as disclosed in Lakowicz to increase the signal of the external fluorophores covalently coupled to the disclosed free probes that are used in the methods disclosed by Lockhart. Attention is also directed to MPEP 2145 and 2123, which state that a "teaching away" requires an active discouragement or disparagement of the proposed solution. It is also noted that the Lakowicz expressly suggests applying the disclosed methods of metal-induced fluorescence enhancement to nucleic acid hybridization assays conducted using external fluorescent labels (pages 102-103).

Applicant further argues that Lockhart only teaches the use of external fluorophores and does not teach detection of target nucleic acids based on intrinsic DNA fluorescence, and that Lakowicz discourages the use of a fluorophore and does not attach probe sequences to metal particles as required by the claims (pages 12-13). Applicant also argues that the combining the teachings of Lockhart and Lakowicz would render Lockhart unsuitable for its intended purpose (pages 12-13).

This argument was not persuasive, because as discussed above, the ordinary artisan would have been motivated by the teachings of Lakowicz to sandwich the external fluorophore contained in the free probe of Lockhart between metallic particles to enhance its signal. Doing so would not cause the method of Lockhart to depend on the detection of intrinsic DNA fluorescence and also would not render the method of Lockhart inoperable or unsuitable for its intended purpose. Rather, application of the teachings of Lakowicz to the method of Lockhart would have improved the method by increasing its sensitivity and enhancing the signal obtained from the external fluorophore contained in the free probe. It is also noted that the teachings of Lakowicz clearly indicate that metallic particles can be used to enhance the fluorescence properties of external fluorophores, such as rose bengal and rhodamine B (see Figures 3-4 on page 97). The teachings of Lakowicz also suggest suitable distances for placement of the fluorophore to maximize metal-induced enhancement of the fluorescence (page 98). It would have been well within the capabilities of the ordinary artisan to apply these teachings of Lakowicz to the methods taught by Lockhart, since all that would be required is selection of a suitable external fluorophore and placement of the fluorophore at a suitable distance from the surface of the array. Since Lakowicz provided explicit guidance as to suitable external fluorophores and optimal metal-fluorophore distances, the ordinary artisan would have had a reasonable expectation of success in using metallic particles to enhance the fluorescence of the external fluorophores used in the methods disclosed by Lockhart. Furthermore, in contrast to Applicant's arguments, the fluorophores taught by Lockhart are not required to be located at the terminus of the free probes. Lockhart does not impose such a limitation on the probes, and the ordinary artisan would have recognized that the location of the fluorophore could be altered (e.g. to an internal position on the free probe of Lockhart), if necessary to provide a suitable distance between the fluorophore and metallic particles. The only requirement imposed on the probes by Lockhart is that they are able to undergo ligation (page 10, lines 3-13). Since the synthesis of oligonucleotide probes having internal fluorescent labels was routine in the art (see, for example, pages 40 and 42 of Lockhart), an ordinary artisan would have had a reasonable expectation of success in modifying the position of the external fluorophore contained in the free probes of Lockhart if necessary to apply the teachings of Lakowicz to the utmost advantage.

Finally, Applicant argues that the teachings of the additional secondary references (Cao and Qi) do not remedy the deficiencies of the Lockhart and Lakowicz references (pages 13-14). This argument was not persuasive, because these references are only relied upon to establish that the ordinary artisan would have had a reasonable expectation of success in attaching oligonucleotides to silver particles and to provide motivation for detecting *B. anthracis* nucleic acids, respectively.

Since Applicant's arguments were not persuasive, upon entry of the proposed amendment, claims 1, 5-10, 12-16, 18, 20-22, and 24-27 would remain rejected under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of the cited references.

Regarding the rejection of claims 1, 4-10, 12-16, 18-22, and 24-27 under 35 U.S.C. 103(a) as being unpatentable over Cao as evidenced by Malicka and Lukomska in view of Lakowicz I and further in view of Lakowicz II, Applicant argues that the combined teachings of the cited references do not render the claimed methods obvious. In particular, Applicant first argues that the Cao reference teaches away from the claimed methods (page 14), and that there is no motivation to combine the teachings of Cao with those of the additional secondary references cited in the rejection (pages 14-16). Applicant also argues that the teachings of Lakowicz II do not remedy the deficiencies of the combination of Cao and Lakowicz II (page 18).

This argument was not persuasive, because the motivation to combine the references has been clearly set forth in the rejection. As discussed previously, the ordinary artisan would have been motivated to sandwich the Cy3 fluorophore used in the method of Cao between metal particles, such as a metal colloid, and measure fluorescence emission from the fluorophore, as taught by Lakowicz I, since Lakowicz I and Lakowicz II taught that the fluorescence signal of a low quantum yield fluorophore could be enhanced by sandwiching the fluorophore between metal particles (see above). Since Lakowicz II taught that fluorescence enhancement by metal particles was analogous to surface-enhanced Raman spectroscopy (page 878) and since the methods of Lakowicz I and Lakowicz II were directed to enhancing the fluorescence of an extrinsic fluorophore conjugated to a nucleic acid (see above), an ordinary artisan would have been motivated to utilize either of these analogous detection methods to detect *Bacillus anthracis* in the method of Cao with a reasonable expectation of success. It is also noted that combination of the cited references does not render Cao unsuitable for its intended purpose or change the principle of operation of the method disclosed by Cao as argued by Applicant (see page 17). Rather, application of the teachings of Lakowicz I and II to the hybridization-based *B. anthracis* detection method disclosed by Cao would result in an improved hybridization-based *B. anthracis* detection method having increased sensitivity due to the metal-induced enhancement of the fluorescence of the Cy3 fluorophore used in the method of Cao. Substituting metal-enhanced fluorescence detection as taught by Lakowicz I and II for the SERS detection taught by Cao would also not change the principle of operation of the method of Cao, since the method suggested by the combined teachings of the cited references would still utilize a sandwich hybridization assay and an observable optical signal to detect the presence of *Bacillus*

anthracis in a sample. It is further noted that the teachings of Cao do not constitute a teaching away from the proposed modification as argued by Applicant, because the combined teachings of Lakowicz I and II would have indicated to the ordinary artisan that the potential difficulties related to the use of external fluorophores described by Cao at page 1536 would have been obviated by sandwiching the fluorophore between metal particles as suggested by the combined teachings of Lakowicz I and II.

Applicant also argues that the rejection does not consider the invention as a whole (pages 16-17). This argument was not persuasive, because the combined teachings suggest the claimed invention as a whole. The claimed invention as a whole appears to be the use of metal particles to sandwich an external fluorophore placed on the free probe used in a sandwich hybridization assay to detect the presence of *Bacillus anthracis* in a sample. The prior art of Cao teaches the use of a sandwich hybridization assay and SERS to detect the presence of *Bacillus anthracis* in a sample. Cao does not teach sandwiching the fluorophore between metal particles as required by the claims; however, the teachings of Lakowicz I and II would have suggested this modification to the ordinary artisan. Accordingly, the claimed invention as a whole is *prima facie* obvious in view of the combined teachings of the cited references.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning (page 17), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, as discussed in greater detail above, the rejection only relies upon the teachings present in the cited references and not Applicant's disclosure, and accordingly, the rejection is proper.

In response to applicant's argument that the examiner has combined an excessive number of references (pages 18-19), reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Finally, Applicant argues that the instant application was previously assigned to a different examiner, and that the present examiner has not given full faith and credit to the previous examiner's work as required by MPEP 704.01 (pages 19-20). Applicant's remarks concerning this point have been considered. However, it is noted that the claims have been amended since the time of the first action on the merits, and the present rejections have been made to properly address the claim amendments. Such action is not considered to be improper.

Since Applicant's arguments were not persuasive, upon entry of the proposed amendment, claims 1, 5-10, 12-16, 18, 20-22, and 24-27 would remain rejected under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of the cited references.